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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,021	03/29/2002	Mart Loog	PL-9915	4673

22840 7590 03/23/2004

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,021	LOOG ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☒ Claim(s) *2 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Sweeden on May 17, 1999. It is noted, however, that applicant has not filed a certified copy of the SE 9901807-9 application as required by 35 U.S.C. 119(b).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claims 2 and 9 are objected to because of the following informalities: For ease of reading, it is suggested that part (a) in claim 2 be changed from "a structure inhibiting binding of..." to "a structure that inhibits the binding of.." Likewise, it is suggested that part (d) of claim 2 be changed from "N is aninhibitor competitively binding ..." to "N is an inhibitor that competitively binds.." In claim 9, it is suggested that "N is a nucleotide structure comprising a nucleotide structure" to "N comprises a nucleotide structure" to avoid redundancy. Appropriate correction is required.

Claim Rejections - 35 USC§ 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is rejected because the phrase "protein/peptide" is vague and indefinite. It is unclear if the phrase means "a protein or a peptide" or if the slash mark between the two words signifies some type of complex between a protein and a peptide.

Claims 4 and 5 are rejected because the term "determinants" is vague and indefinite. The nature and number of factors that govern the "determinants" is unclear.

Claim 11 is rejected because the phrase "in the form of a derivatized carboxylic acid" is vague. It is unclear how many and what types of "forms" are claimed. Likewise, the nature and number of "derivatives" is unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 9, 10 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (1977).

Lee et al. teach the attachment of a bifunctional dinucleotide, AMP-ATP, to a solid phase. The dinucleotide derivative comprises disubstitution at the N6- and C8-positions of AMP for purification of kinases. A diaminohexyl linker joins the ATP and

AMP moieties. Another diaminohexyl linker anchors the AMP portion of the molecule to the solid phase (page 31, introduction and page 33, Fig. 1). The AMP-ATP bifunctional affinity ligand was used for the purification of mouse kidney kinases and dehydrogenases from a homogenate (p. 32, third paragraph and page 37, affinity chromatography section). Lee et al. are silent regarding the locations where the AMP-ATP derivative binds to the kinase and if said derivative is an inhibitor of kinases. However, the disclosed AMP-ATP ligands are inherently inhibitors because Lee et al. do not report a reaction between the kinases that were being purified to the disclosed affinity ligands.

The disclosure by Lee et al meets the limitations of claims 1 and 2 because the ligand reported by Lee et al. is bifunctional. The broadest reasonable meaning of "bifunctional" is that a molecule is doubly substituted, as is the N6-, C8- AMP derivative reported by Lee et al. Claim 2 of the instant application defines how the C and N moieties of the claimed ligand bind kinase substrates. Lee et al. is silent regarding this limitation. Lee et al. teach the employment of bifunctional linker to purify a kinase from a liquid. This disclosure meets the process limitations in the claimed method because the composition is being used in the same steps to purify a kinase. The mechanism of binding of the kinase by the affinity ligand is an inherent feature of the process. The mechanism of the process of purification does not bear on the patentability of the claimed process. Further characterization of what occurs in a known method does not impart patentability because the outcome of the method is the same. See Ex parte Novitski, 26 USPQ 2nd 1389 (BOPA 1993). The disclosure by Lee et al. meets claims 9

and 10 because the ATP moiety taught by Lee et al. bears phosphoryl groups that can phosphorylate ATP and GTP. The 5' carbon of said nucleotide is bound to the diaminohexyl linker. The Sepharose carrier used by Lee et al. is inherently insoluble in water (claim 14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (1997) in view of Lee et al. (1977), Olsen et al. (1989), Ricouart et al. (1991) and Iltzsch et al. (1995).

Rosse et al. disclose the design and synthesis of modified tri- and tetrapeptides as bisubstrate inhibitors of epidermal growth factor receptor (EGF-R) protein tyrosine kinase (RKT). (According to the prior art, bisubstrate is equivalent to bifunctional.) The design on the inhibitors was based on the separate binding interactions of the kinase for ATP and the protein substrate (p. 654-655). The inhibitors consisted of adenosine linked to combinations of tri- and tetrapeptides with a triphosphate mimic or spacer. The illustration of the transition state of proposed bisubstrate inhibitors is shown on page 655 (this disclosure covers structure in claim 2). The bisubstrate inhibitor comprises a tri- or tetrapeptide as the mimic for the protein substrate. The adenosine moiety binds to

the ATP binding domain of the kinase (covers claims 9 and 10). The two moieties are connected by a linker, which are disclosed at the bottom of the page. The peptide sequence Glu-Tyr-Leu was derived from a consensus sequence for the phosphorylation site of natural substrates to EGF-R and the tetrapeptide sequence, Glu-Tyr-Leu-Arg, corresponds to the major autophosphorylation site of the EGF-R (covers claims 3-6 and 15-17). Rosse et al. report that the bisubstrate analogs were inhibors of EGF-R (page, 659, third paragraph).

Rosse et al. do not teach that the bisubstrate inhibitors can be utilized as an affinity ligand for purification of kinases, that the peptide chain comprises at least two acidic and/or basic amino acids which are aspartic acid and arginine, respectively, that the adenosine moiety is a 5'-carboxylic acid derivative, that the linker is a peptide chain that can be composed of non-alpha and/or non-L amino acids or that the bisubstrate inhibitor is attached to an insoluble carrier.

Olsen et al. disclose that a polypeptide derived from rabbit muscle protein kinase is an effective inhibitor of kinases in vitro. The 18-residue peptide, referred to as PKIP, comprises three arginine, one aspartic acid and several hydrophobic amino acids (covers claims 7 and 8). PKIP was linked to a carrier that is insoluble in water (covers claim 14, see p. 18662, Experimental section). The polypeptide served as an affinity ligand for the purification of isoforms of cAMP protein kinase (p. 18663, right column, fourth paragraph).

The disclosure of Lee et al. is discussed vide supra. Lee et al. teach that a bifunctional ligand having AMP and ATP moieties is more effective for the purification of

kinases from a homogenate than an affinity-Sepharose material having only one AMP ligand (p. 37, right column, last paragraph). Further, Lee et al. assert that bifunctional kinase inhibitors are useful as ligands for affinity chromatography (p. 39).

Riacouart et al. disclose the design and testing of potent protein kinase inhibitors based on a combination, in the same structure, that mimics of both the ATP and protein binding sites. Various isoquinoline sulfonamides, which bind to the ATP domain, were linked to a dipeptide which binds to the protein binding. A flexible linker consisting of two beta-alanine residues linked the two moieties (meets claims 12-13, page 74, left column, second paragraph).

Iltzsch et al. disclose the structure-activity relationship for the binding of 128 modified purine nucleoside analogs to a kinase from the parasite, *T. gondii*. The inhibitions constant, Ki, for the binding of the analogs to the kinase were evaluated. Iltzsch report that adenosine 5'-carboxylic acid had a Ki of 1,100 uM (p. 1505, entry 99 in Table 1, covers claim 11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the bisusbstrate, peptide-linker-ATP, inhibitors disclosed by Rosse et al. as affinity ligands for kinase purification. At the time, the use of affinity chromatography with ligands having one binding interaction with a kinase was well known (Lee et al.). The ordinary artisan would have been motivated to use the disclosed peptide-linker-ATP inhibitors as affinity ligands for chromatography because ligands having two kinase-binding moieties had been shown by Lee et al. to be superior for the purification of kinases compared to affinity ligands having only one binding interaction

with a kinase. The ordinary artisan would have had a reasonable expectation that the peptide-linker-ATP compounds would function successfully as ligands for affinity chromatography for several reasons. Olsen et al. and Lee et al. demonstrated that affinity ligands consisting of inhibitors having peptide or nucleotide structures were effective for kinase isolation. Rosse et al. demonstrated that the peptide-linker-ATP compounds were good inhibitors of kinases. Hence, the ordinary artisan could expect that the bifunctional peptide-linker-ATP compounds would function effectively as affinity ligands for the isolation of kinases.

It would have been obvious to one of ordinary skill in the art to modify the disclosed peptide-linker-ATP ligands with at least two arginine residues in the peptide moiety, employ an adenosine residue with a 5'-carboxy group, or using non-alpha and/or non-L amino residues in the linker to improve the inhibition properties of the peptide-linker-ATP bisubstrate inhibitor. The references teach that the claimed variations in affinity ligands for kinase purification were well known. Rosse et al. and Riacouart et al. teach that adjusting the bisusbstrate inhibitor structure to improve inhibitor status was also well known. Hence, the ordinary would have had a reasonable expectation that the claimed modifications would be effective for the claimed bifunctional inhibitor. The use of insoluble carriers for affinity ligand purification is standard practice in the art.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loog et al. (May 17, 1999) in view of Lee et al. (1977).

Loog et al. disclose protein kinase bisubstrate inhibitors comprising a 5'-carboxylic acid adenosine derivative combined with a linker that is attached to a peptide that is derived from a protein kinase consensus sequence. Said peptide chain comprises at least two acidic and/or basic amino acids which are aspartic acid and arginine, respectively. The linker is a peptide chain that can be composed of non-alpha and/or non-L amino acids. Loog et al. teach that the disclosed bisubstrate analogs were effective inhibitors of protein kinases because of the ability of the compounds to bind at two separate sites of a kinase. Loog et al. further assert that the disclosed compounds may be selectively targeted toward particular protein kinases proceeding from their peptide substrate specificity motif (p. 1451).

Loog et al. do not teach that the disclosed 5'-carboxylic acid adenosine-linker-peptide compounds can be employed as affinity ligands for the isolation of protein kinases from a liquid or that said ligand can be attached to a water-insoluble carrier.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the bisusbstrate, peptide-linker-ATP, inhibitors disclosed by Loog et al. as affinity ligands for kinase purification. At the time, the use of affinity chromatography with ligands having one binding interaction with a kinase was well known. The ordinary artisan would have been motivated to use the disclosed peptide-linker-ATP inhibitors as affinity ligands for chromatography because ligands having two kinase-binding moieties had been shown by Lee et al. to be superior for purification of kinases compared to affinity ligands having only one binding interaction with a kinase. The ordinary artisan would have had a reasonable expectation that the peptide-linker-

ATP compounds would function successfully as ligands for affinity chromatography for several reasons because peptide-linker-ATP compounds disclosed by Loog effectively bind to kinase and were good inhibitors of kinases. Hence, the ordinary artisan could expect that the bifunctional peptide-linker-ATP compounds would function effectively as affinity ligands for the isolation of kinases. The use of insoluble carriers for affinity ligand purification is standard practice in the art.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. It is further noted that the foreign priority papers have not been filed in the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEAN C. WITZ
PRIMARY EXAMINER